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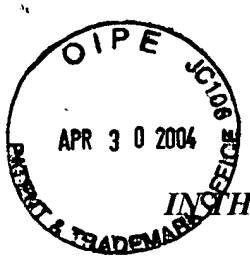

PATENT
Atty. Dkt. No. SALK1650-2
(088802-2753)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Marc R. Montminy

Title: METHODS FOR TREATING DIABETES MELLITUS

Appl. No.: 09/515,276

Filing Date: 02/29/2000

Examiner: D. Wortman

Art Unit: 1648

CERTIFICATE OF MAILING
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Germaine Sarda
(Printed Name)

(Signature)

April 27, 2004
(Date of Deposit)

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Transmitted herewith are the following:

[**X**] Appeal Brief (33 pages) *In Triplicate*;

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The required fees are calculated below:

[X]	Notice of Appeal Fee	$330.00
[ ]	Extension month:	$0.00
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[X]	Small Entity Fees Apply (subtract ½ of above):	$165.00
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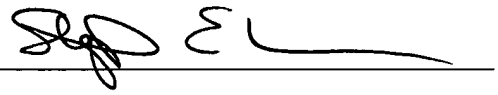
[**X**] Please charge Deposit Account No. 50-0872 in the amount of $165.00 . A duplicate copy of this transmittal is enclosed.

[**X**] The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date: April 27, 2004

By 

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Marc R. Montminy
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Appl. No.:	09/515,276
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April 27, 2004
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APPEAL BRIEF

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Sir:

Applicant (herein, "Appellant") submits this Appeal Brief in response to the Final Rejection of claims 1-7, 12 and 17-33. This Appeal Brief, submitted in triplicate, is accompanied by the requisite fee set forth in 37 C.F.R. § 1.17(c). If this fee is incorrect or if any additional fees are due in this regard, please charge or credit Deposit Account No. 50-0872 for the appropriate amount.

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Table of References

Real Party in Interest

The real party in interest in this appeal is The Salk Institute for Biological Studies, which is the assignee of the present application.

Related Appeals and Interferences

Appellant is not aware of any related appeals or interferences that may have a bearing on the board's decision in the pending appeal.

Status of Claims

Claims 1-7,12 and 17-33 were finally rejected by the Examiner on November 28, 2003. A Notice of Appeal for claims 1-7, 12 and 17-33 was timely filed by Appellant on February 27, 2004. The text of claims 1-7,12 and 17-33 are attached hereto as Appendix A.

Status of Amendments

All Amendments have been indicated as entered.

Summary of The Invention

Appellant discovered that intracellular interactions exist between cyclic AMP (cAMP) responsive transcriptional activator ("CREB") and CREB binding protein ("CBP"), a protein that binds to the phosphorylated (i.e., activated) form of CREB and mediates cAMP responsive transcription. From this discovery, Appellant devised methods of identifying compounds that would act as inhibitors of this interaction and appreciated that such compounds would be useful in the treatment of diabetes mellitus, modulation of glucose metabolism and inhibition of the expression of the enzyme phosphoenylpyruvate carboxykinase (PEPCK) (see, e.g., Summary of

the Invention). At the time the instant patent application was filed, is was not known that cAMP was a critical gene transcription mediator in these diseases and conditions and that interaction between CREB and CBP could be used to control phosphorylation of cAMP, thereby affecting diabetes mellitus, glucose metabolism and PEPCK enzyme expression.

Thus, the present invention relates in part to methods for treating diabetes mellitus by administering a compound that inhibits the interaction between CREB and CBP. Claims 12 and 17 each specify a method by which inhibitory compounds useful for this purpose are identified.

The present invention also relates in part to methods for modulating glucose metabolism in an individual by administering a compound that inhibits the interaction between CREB and CBP.

The present invention further relates in part to methods for inhibiting expression of phosphoenylpyruvate carboxykinase (PEPCK) enzyme in an individual by administering a compound that inhibits the interaction between CREB and CBP.

Issues

1. Whether a prima facie case of lack of written description has been established by the Examiner for the claimed methods of treating diabetes mellitus when the application discloses active compounds and their use and, if such case has been stated, whether Appellant has overcome the rejection.

2. Whether a prima facie case of a lack of enablement has been established by the Examiner for the claimed methods of treating diabetes mellitus where the application provides a novel mechanism of action and the Examiner fails to offer scientific evidence that contradicts the

inventive mechanism of action and, if such case has been stated, whether Appellant has overcome the rejection.

3. Whether a prima facie case of lack of written description has been established by the Examiner for the claimed method of modulating glucose metabolism in an individual when the application discloses active compounds and their use and, if such case has been stated, whether Appellant has overcome the rejection.

4. Whether a prima facie case of lack of enablement has been established by the Examiner for the claimed methods of modulating glucose metabolism in an individual where the application provides a novel mechanism of action and the Examiner fails to offer scientific evidence that contradicts the inventive mechanism and, if such case has been stated, whether Appellant has overcome the rejection.

5. Whether a prima facie case of lack of written description has been established by the Examiner for the claimed invention of inhibiting expression of phosphoenylpyruvate carboxykinase (PEPCK) enzyme when the application discloses active compounds and their use and, if such case has been stated, whether Appellant has overcome the rejection.

6. Whether a prima facie case of lack of enablement has been established by the Examiner for the claimed methods of inhibiting expression of phosphoenylpyruvate carboxykinase (PEPCK) enzyme where the application provides a novel mechanism of action and the Examiner fails to offer scientific evidence that contradicts the inventive mechanism and, if such case has been stated, whether Appellant has overcome the rejection.

Grouping of Claims

Claims 1-7,12 and 17, all directed to a method of treating diabetes mellitus, all stand or fall together.

Claims 18-24 and 33, all directed to a method of modulating glucose metabolism in an individual, all stand or fall together.

Claims 25-32, all directed to a method of inhibiting expression of phosphoenylpyruvate carboxykinase (PEPCK) enzyme in an individual, all stand or fall together.

Argument

35 U.S.C. § 112, First Paragraph, Written Description Rejection

The rejection of claims 1-7, 12 and 17-34 under 35 U.S.C. § 112, first paragraph for allegedly lacking written description is respectfully submitted to be in error for the following reasons.

Applicable legal standard

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.* A careful analysis of the written description requirement provided by the Patent and Trademark Office in its *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶1, "Written Description" Requirement*, reveals that an adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." 66 Fed. Reg. 1099, 1105 (2001) (emphasis added).

The specification provides adequate written description for claims 1-7, 12 and 17, directed to treatment of diabetes mellitus.

The crux of the rejection, in the Examiner's words, appears to be that the "specification does not describe or disclose the structure of even one compound that has been identified by Appellant's method and treats diabetes." Paper No. 23, page 5. The Examiner alleges that only functional characteristics are given, that being "to disrupt or inhibit binding of CREB to CBP." *Id.*

First, the Examiner has cited to no law for the extreme proposition that the written description requirement for a method claim requires a chemical structure, especially under the facts of the present application, which contemplates use of a compound, the identity of which can be determined by methods extensively described and admitted by the Examiner to be enabling, and where exemplary compounds are disclosed in the specification. A functional description of the compound and a method of identifying the compound, which method the Examiner admits is enabled, provides sufficient description of the method. Furthermore, the specification discloses the structure of many inhibitory compounds in the paragraph bridging pages 15 and 16, quoted below.

> Compounds which are capable of inhibiting activation of cAMP and mitogen responsive genes, and hence can be identified by the invention assay method, include antibodies raised against the binding domain of the protein set forth in SEQ ID NO:2, antibodies raised against the binding domain of CBP-like compounds, and the like. Presently preferred antibodies are those raised against a polypeptide fragment comprising amino acid residues from about 461 up to 661 of the protein set forth in SEQ ID NO:2; with antibodies raised against a polypeptide fragment comprising amino acid residues from about 634 up to 648 of the protein set forth in SEQ ID NO:2 (this subfragment is also set forth specifically as SEQ ID NO:3), being especially preferred. Alternatively, antibodies which are raised against the amino acid residues surrounding residue 600 of CBP (see SEQ ID NO:2) or antibodies which inhibit the phosphorylation of residue 133 of CREB are also desired (see, for example, Parker et al., Mol Cell Biol (1996) 16(2):694-703).

The above passage describes antibody compounds that disrupt CREB:CBP interaction and, hence, inhibit activation of cAMP and mitogen responsive genes. The structure of an antibody is well known and is described in reference to what it binds. Furthermore, page 17, first

full paragraph of the specification, discloses the structure of additional inhibitory compounds as quoted below.

> Alternative compounds which are capable of inhibiting activation of cAMP and mitogen responsive genes include polypeptide fragments comprising amino acid residues from about 461 up to 661 of the protein set forth in SEQ ID NO:2. Polypeptide fragments comprising amino acid residues set forth specifically as SEQ ID NO:3 or KIX polypeptide fragments having a mutation at residue 600 (Arg-600), set forth in SEQ ID NO:2, are preferred, while KIX polypeptide fragments substituting Gln for Arg-600 are presently most preferred. Other polypeptide fragments contemplated for use in the practice of the present invention include those comprising the KID domain, preferably those comprising residue 133 of CREB. In the most preferred CREB polypeptide fragment, serine residue 133 is mutated to an amino acid residue which can not be phosphorylated. Other compounds which inhibit CREB activity (i.e., phosphorylated-Ser133) by binding to CBP include adenovirus E1A oncoprotein (Nakajima et al. Genes Dev (1997) 11(6):738-747), and the like. Those of skill in the art will readily recognize other polypeptide fragments which will readily inhibit the formation of CREB:CBP complex employing such assays as those disclosed herein.

This passage describes peptide fragment inhibitory compounds including the KIX and KID domains and mutated forms of the peptides. Precise structures of the compounds are provided by reference to specific sequences (see citations to SEQ ID NOS.). The adenovirus E1A oncoprotein is also mentioned as a CREB:CPB interaction inhibitor.

In response, the Examiner argues that the claims "do not recite that antibodies, peptides or adenovirus EIA are administered as a treatment." Paper No. 25, page 4. Whether there are claims that recite this embodiment is irrelevant to the question of written description. As

indicated by the quoted passages above, the specification considers these compounds to be suitable inhibitors and the specification does not indicate any unsuitability of such compounds for use in the therapeutic methods of the invention.

The Examiner further argues that there is no description for administering an effective amount of "these types of compounds" [i.e. the exemplified compounds]. Paper No. 25, page 4. However, the specification at page 21, lines 21-33 (quoted below) clearly describes what constitutes an effective amount and how it can be determined in a general sense for any inhibitory compound.

> As employed herein, the phrase "effective amount" refers to levels of compound sufficient to provide circulating concentrations high enough to modulate the expression of gene(s) mediated by members of the steroid/thyroid superfamily of receptors. Such a concentration typically falls in the range of about 10 nM up to 2 μM; with concentrations in the range of about 100 nM up to 500 nM being preferred. Since the activity of different compounds described herein may vary considerably, and since individual subjects may present a wide variation in severity of symptoms, it is up to the practitioner to determine a subject's response to treatment and vary the dosages accordingly.

The Examiner's final rejection, which cited to only the first sentence of the above paragraph, fails to acknowledge that the teaching in the specification supporting the administration of an effective amount is not limited to any particular type of inhibitory compound. As such, it must be concluded that such teaching would be understood to apply to the exemplified compounds as well as to compounds that one could identify using the methods of selection that have been admitted by the Examiner to be enabled. The Examiner finally

concludes that no written description is present because 1) CREB:CPB interaction occurs within a nucleus, and 2) there is no description of compounds identified by Appellant's method that have been administered to an individual at levels of compound sufficient to provide circulating concentration high enough to modulate the expression of genes(s) mediated by members of the steroid/thyroid superfamily of receptors. Paper No. 25, page 4-5. The Examiner's conclusion constitutes nothing more than a demand for clinical data demonstrating that the claimed method works in humans. This is an improper standard in any event; such a demonstration is not required by statute or law.

Thus, the application fully describes a method of diabetes treatment and modulating glucose metabolism or inhibiting PEPCK through the administration of compounds that disrupt interaction of CREB with CBP. The application also describes numerous exemplary compounds. It is respectfully submitted that one skilled in the art would agree that the inventor was "in possession of the claimed invention." Because the written description requirement of 35 U.S.C. § 112, first paragraph, has been met, Appellant respectfully requests that the rejection be reversed as to claims 1-7,12 and 17.

The specification provides adequate written description for claims 18-24, and 33 directed to methods of modulating glucose metabolism and claims 25-32, directed to methods of inhibiting expression of PEPCK

Unlike claims 1-7, 12 and 17, which are directed to methods of diabetes treatment, claims 18-24 and 33 are directed to methods for modulating glucose metabolism in an individual, and claims 25-32 are directed to methods of inhibiting the expression of PEPCK enzyme in an individual. The Examiner applies the same argument for lack of written description of the

diabetes treatment claims to claims 18-33 because "all the claims either explicitly recite treatment of human diabetes *per se* or encompass treatment of human diabetes." Paper No. 25, page 4. The Examiner explains this reasoning on the fact that dependent claims 31 and 33 specify that the individual is suffering from diabetes. *Id.*

It is respectfully submitted that the written description rejection is improperly founded on a mischaracterization of claims 18-33 . None of these claims encompasses "treatment of human diabetes" as alleged by the Examiner. Rather, claims 18-24 and 33 expressly state that the method is for modulating glucose metabolism in an individual, while claims 25-32 expressly state that the method is for inhibiting expression of phosphoenylpyruvate carboxykinase (PEPCK) enzyme in an individual. The fact that an individual may be suffering from diabetes mellitus does not change the stated purpose of the claims (i.e., a method of modulating glucose metabolism and a method of inhibiting expression of PEPCK).

Furthermore, the, application fully describes a method of modulating glucose metabolism and of inhibiting PEPCK through the administration of compounds that disrupt interaction of CREB with CBP. For example, specification at page 20, lines 1-11, refers to modulating gluconeogenesis and/or hyperglucagonemia by "employ[ing] compounds which disrupt the formation of CREB:CBP complexes as detailed above, thus inhibiting the transcription of PEPCK or glucogon gene." The specification also describes numerous exemplary compounds and how to use them for inhibiting the CREB:CBP complex. It is respectfully submitted that one skilled in the art would agree that the inventor was "in possession of the claimed invention."

Because the written description requirement of 35 U.S.C. § 112, first paragraph, has been met, Appellant respectfully requests that the rejection be withdrawn as to claims 18-33.

35 U.S.C. § 112, First Paragraph, Enablement Rejection

The rejection of claims 1-7 and 12 and 17 for allegedly failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, is respectfully submitted to be in error for the following reasons.

Applicable legal standard

The standard for determining enablement is whether the specification as filed provides sufficient information to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Furthermore, under Patent Office practice, a patent specification is considered to be in compliance with the enabling requirement of § 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein. Thus, the Examiner carries the initial burden to substantiate a rejection for lack of enablement. In *re Marzocchi*, 439 F.2d 220, 223-24 (CCPA 1971). In accordance with the burden, the Patent Office must explain why the truth or accuracy of any statement in the specification is doubted and "back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." Id.; see also, *In re Richard Sichert*, 566 F2.d 1154, 1161 (CCPA 1977)) ("The PTO has cited to no evidence or reference that contradicts or is inconsistent with any supporting statement of the disclosure.").

The specification provides an enabling disclosure for Claims 1-7, 12, and 17, directed to methods of treating diabetes mellitus.

Appellant respectfully submits that no prima facie rejection for enablement has been stated. The rejection imposes an improper standard of enablement that does not comport with settled law when concluding that Appellant's submission of proof of enablement in the form of the Mayr et al. reference is allegedly insufficient because it "does not teach that a compound identified by Appellant's method has a beneficial effect when used to treat diabetes." Paper No. 23, page 10 (see also similar statement bridging pages 10 and 11 regarding the Herzig et al. reference). It is respectfully submitted that a proper review and application of the seven Wands factors demonstrates enablement of the claims 1-7, 12 and 17.

Wands Factor 1: Nature of the Invention

The claims at issue are directed to a method for treating an individual suffering from diabetes mellitus by administering a compound that disrupts the interaction between CREB and CBP. The compounds are identified by functional language or by an assay which describes how to identify useful compounds. As already discussed above, the specification describes numerous exemplary compounds including antibodies and peptides that will bind either to CREB or to CBP and will disrupt the interaction which is critical to activation of cAMP and mitogen responsive genes involved in diabetes. The Examiner acknowledges Appellant's description of this Wands factor. Paper No. 25, page 7.

Wands Factor 2: State of the Prior Art

The prior art is replete with examples where drugs that affect intracellular events have a beneficial impact in disease treatment. Nearly the entire pharmaceutical industry is based on this principle. Particularly relevant to the instant case is the well established understanding in the prior art of the toxic role played by elevated glucose levels in diabetic individuals. See e.g., Rossetti "Glucose Toxicity: the implications of hyperglycemia in the pathophysiology of diabetes mellitus" *Clin Invest Med* 18(4): 225-260 1995 (citing on page 225 to references 1-7 for the proposition that there is "substantial evidence linking hyperglycemia to the development and progression of complications associated with diabetes [1-7]") (attached as Exhibit A to Response dated 9/11/03); *see also* Flatt et al. *Biochemical Society Transactions* 22: 18-23 (1994) (discussing glucose toxicity and role of glycation therein; p.24) (attached as Exhibit B to Response dated 9/11/03). Thus, Appellant's method of treating diabetes, which entails reducing hyperglycemia by modulating aspects of glucose metabolism (through disruption of the fundamental CREB:CBP interaction), addresses what one skilled in the art would consider to be a predictable route to treating diabetes.

In contrast, the Examiner's sole effort at establishing the state of the prior art is to cite to the Merck Manual, 17th edition, pages 174-176 that discuss treatment of diabetes. It is respectfully submitted that the Merck Manual provides, at best, an incomplete understanding of the prior art since the Merck Manual is not current and does not include relatively recent innovations. Indeed, as previously demonstrated by Appellant (Response 9/11/03), the Merck Manual is not close to being a reliable source for the latest in diabetes treatment methods.

Instead the Merck Manual only discusses long established methods of diabetes treatment, mainly treatment using insulin, sulfonylureas, and certain anti-hyperglycemic drugs.

Appellant has further supported this view by establishing the fact that the Merck Manual fails to mention any of a larger number of recently patented diabetes treatment methods (a search for "diabetes," "treat" and "method" as claim terms identified 89 issued U.S. patents; a random sampling of these showed that many are directed to new methods of diabetes treatment that are not mentioned in the Merck Manual). For example, U.S. Patent No. 5,561,110 to Michaelis et al. describes and claims carnosine and peptide analogues of carnosine which are useful for treating diabetes mellitus. According to Michaelis et al., carnosine scavenges reducing sugars in blood, reducing the level of protein and lipid glycation and toxic effects caused thereby. See Cols. 2 and 3. The Merck Manual cited by the Examiner does not mention treatment with carnosine. In addition, U.S. Patent No. 5,674,900 to Ubillas et al. describes and claims a novel terpenoid-type quinone which is useful for treating diabetes mellitus. According to Ubillas et al. "[n]o compound resembling the structure of the claimed compounds has in any way been associated with the usefulness in the treatment of diabetes mellitus or its sequelae." Col. 3, lines 22-25. The Merck Manual cited by the Examiner also does not mention treatment with terpenoid-type quinones. It is respectfully submitted that the same can be said for the new methods of diabetes mellitus described in U.S. Patent Nos. 5,691,386; 5,700,795; 5,384,032; 5,888,507; 6,146,653; 6,300,349; 6,323,314, all of record in the case.

Accordingly, as shown by a proper review of the state of the prior art, it can be seen that Appellant's method of treating diabetes mellitus addresses what one skilled in the art would consider to be a predictable route to treating diabetes. In contrast, the Examiner's evaluation of

the state of the prior art being limited to citation of the Merck Manual, which discusses only long established methods for treating diabetes mellitus, constitutes a clearly deficient analysis of this Wands factor.

After several years of prosecution on this issue, the Examiner now admits that "potential treatments or new treatments may not be described in the Merck Manual." Paper No. 25, page 7. Rather than withdrawing the rejection at this point after abandoning the only evidence offered to support a prima facie case of non-enablement, the Examiner maintains the rejection by shifting (improperly) the burden of proof of enablement to Appellant. Paper No. 25, page 7.

Wands Factor 3: Level of One of Ordinary Skill

Appellant respectfully submits that the level of skill in the art of protein-protein interaction inhibitors and their use in complex diseases such as diabetes is high. Considering the objective evidence of record in its entirety, Appellant respectfully submits that the skilled artisan would acknowledge that the level of skill in the art is high for the treatment of diabetes by administering compounds that affect glucose metabolism. The Examiner acknowledges that the level of skill is high. Paper No. 25, page 7.

Wands Factor 4: Predictability in the Art

Appellant respectfully submits that the art in the relevant field is reasonably predictable. As indicated from the analysis of the state of the art, there is a great deal known about the role of glucose in diabetes and about the beneficial effects of lowering circulating glucose levels. Appellant's discovery that the CREB:CBP interaction is central to the regulation of glucose

metabolism and that compounds which inhibit this interaction are useful in treating diabetes puts the discovery squarely within an approach known to be predictable. The application also provides exemplary inhibitory compounds and methods to identify others that require only routine experimentation.

Considering the objective evidence of record in its entirety, Appellant respectfully submits that the skilled artisan would acknowledge that it would be predictable that administering compounds that disrupt interaction between CREB and CBP would be beneficial to the treatment of diabetes.

The Examiner attempts to establish unpredictability in the field with the following offering:

> Applicant's assertion, unsupported by facts, that the art in the field is "reasonably predictable" is not persuasive, and Examiner's remarks in the previous Office action citing Herzig et al. regarding unpredictability and the amount of experimentation remaining in the field nearly four years after Applicant's effective filing date are reiterated here: The effect of A-CREB on liver gene expression suggests that CREB **may** constitute a ideal target for therapeutic intervention. Although use of dominant negative inhibitor such as A-CREB may not be feasible in this regard, small molecules that block CREB phosphorylation or disrupt recruitment of the CREB coactivator CBP (CREB binding protein) **may** prove effective. Such compounds **may** be particularly beneficial as adjunctive therapy in lowering fasting blood glucose levels in early type II diabetes.

Paper No. No. 25, page 7-8 (emphasis in original). The use of "may" in the sentences above hardly supports a conclusion that Mayr[1] believes the field is unpredictable. The Examiner has

[1] Mayr et al. "Transcriptional Regulation of the Phorphorylation-Dependent

pointed to nothing in Mayr that explains the asserted interpretation. To the contrary, the Mayr reference supports predictability of the field by demonstrating the key principle underlying Appellant's approach to diabetes mellitus treatment. Mayr describes the mechanism by which CREB controls glucose homeostasis, involving phosphorylation of CREB at Ser133, which promotes complexing with the transcriptional co-activator CBP. Mayr, p599, left column and Figure 1a. The Abstract of Mayr states that CREB "functions in glucose homeostasis." These conclusions are consistent with Appellant's disclosure teaching involvement of CREB-CBP complex in diabetes. Viewed in this light, it is respectfully submitted that one skilled in the art would view the Mayr as imparting a positive rather than a negative outlook.[2]

Wands Factor 5: The Amount of Direction or Guidance Present

The instant specification provides methods to identify a compound that inhibits the interaction of CREB with CBP. Included is a description of various cell lines to use and expression vectors to express the interacting proteins in the form of a functional bioassay. In fact, inhibiting compounds are described as already discussed and supported by citation herein above. The working examples of the specification provide further enabling support for compound selection methods. With respect to diabetes treatment, for compounds which meet the

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Factor CREB" Molec. Cell Biol., 2:599, 2001.

[2] The Examiner's reliance on the "may" in Mayr fails to consider its use in context with very lofty goals "an ideal target or "particularly beneficial." (emphasis added)

inventors' criteria, the specification provides a description of suitable routes of administration, methods of formulation, and dosing, the latter including concentration ranges (page 17-18).

The Examiner agrees that the specification teaches inhibitory compounds but argues that the disclosure supporting routes of administration, formulation and dosing are "presented in a general fashion and not directed to methods of treatment with any specific compounds." Paper No. 25, page 8. However, approaches for establishing the proper formulation and routes of administration are considered routine and only a general disclosure need be provided.

Considering the objective evidence of record in its entirety, Appellant respectfully submits that the skilled artisan would acknowledge that the specification provides extensive guidance for making compounds and for using them with a reasonable likelihood of success.

Wands Factor 6: Presence of Working Examples

As already mentioned, the working examples of the specification provide further enabling support for compound selection methods. With respect to diabetes treatment, for compounds which meet the inventors' criteria, the specification provides a description of suitable routes of administration, methods of formulation, and dosing, the latter including concentration ranges (page 17-18). The Examiner takes issue with the disclosure as being limited to prophetic examples. Paper No. 25, page 8. The proper inquiry, however, is not whether the examples are working or prophetic, but rather whether the specification enables the skilled artisan to obtain such effects without undue experimentation. The Examiner argues that the examples in the specification do not correlate with the claimed treatment methods. *Id.* However, the Examiner cites to no scientific reasoning as a basis to question whether the claimed methods of treating

diabetes using an inhibitor of CREB:CBP interaction would be successful in the treatment of diabetes mellitus.

Furthermore, Appellant has cited to the work of Mayr et al. and Herzig et al. ("CREB Regulates Hepatic Gluconeogenesis Through the Coactivator PGC-1" Nature 413:179-183, 2001), as proof of the key principle underlying the claimed method of diabetes treatment. The teachings of Mayr et al., already discussed above, establish the role of CREB:CPB interaction. Herzig et al. ("Herzig") reports that CREB controls glucose homeostasis through expression of gluconeogenic enzymes via the transactivator, PGC-1. Herzig also used normal and diabetic animals to prove that a reduced CREB activity causes fasting hyperglycemia in vivo, a result that Herzig states "is correlated with Type II diabetes." Herzig, page 179 (Abstract).

Therefore, both the Mayr and Herzig articles serve to prove the truth of statements in Appellant's disclosure (i.e., that disruption of CREB-CBP interaction can be used to treat diabetes), and are not offered to supplement the disclosure. See In re Marzocchi, 439 F.2d at 224, n.4 (indicating that references which are not prior art can be used to rebut a prima facie case for lack of enablement if the "question would be regarding the accuracy of a statement in the specification, not whether that statement had been made before.").

Although the key underlying principle for the therapy has been proven to be operable *in* vivo, the Examiner appears to maintain the rejection because the specific exemplified compounds in the application have not actually been used in the therapeutic method. Paper No. 25, page 9. The Examiner is in effect requiring that Appellant demonstrate actual clinical results for treatment of diabetes. This is an improper standard of enablement that does not comport with settled law. It is clearly improper to require Appellant to prove enablement only in the form of

actual data that a compound of the invention has a beneficial effect in the treatment of diabetes. The question is not whether beneficial effects have been generated, as the Examiner suggests; rather, the question is whether the specification enables the skilled artisan to obtain such affects without undue experimentation. The Examiner has cited to no scientific reasoning as a basis to question whether the claimed methods of treating diabetes using an inhibitor of CREB:CBP interaction would be as successful in the treatment of diabetes mellitus as would the approaches used by Mayr et al. and Herzig et al. As has been demonstrated by Appellant, the scientific literature describes that reduction in blood glucose levels is a treatment for diabetes and Mayr and Herzig prove that the principle underlying the present invention will reduce blood glucose levels *in vivo*. The Examiner's reliance on the use of the word "may" in the Mayr reference and on the absence of Appellant's method being cited in the Merck Manual (now admitted to be a deficient source for new methods of diabetes treatment) fall far short of countering the underlying science which has been confirmed in peer-reviewed prestigious publications.

Considering the objective evidence of record in its entirety, the skilled artisan would acknowledge that the working examples of the application support enablement of the claims at issue.

Wands Factor 7: Quantity of Experimentation Necessary

Appellant respectfully submits that the amount of experimentation necessary is not undue. There is no reason to believe that useful inhibitors of the CREB:CBP interaction will not be useful when such compounds reach the targeted components (CREB or CBP) in cells. Only routine experimentation would be needed to identify compounds that function well in this regard.

The Examiner, in contrast, has offered no evidence on this Wands factor. Considering the objective evidence of record in its entirety, Appellant respectfully submits that the skilled artisan would acknowledge that the quantity of experimentation necessary to practice the claimed methods is not undue.

Claims 1-7, 12 and 17 Meet the Enablement Standard of 35 U.S.C. §112, first paragraph.

In view of the objective evidence of record, and the foregoing analysis of the factors set forth in *In re Wands*, Appellant respectfully submits that claims 1-7, 12 and 17 meet the enablement standard of 35 U.S.C. § 112, first paragraph. The Examiner's opinion to the contrary is not founded on a proper Wands analysis and is defective for applying a standard for determining compliance with the enablement requirement that does not comport with the settled law. Because the enablement requirement of 35 U.S.C. § 112, first paragraph, has been met, Appellant respectfully requests that the rejection be reversed with respect to Claims 1-7, 12 and 17.

The specification provides an enabling disclosure for Claims 18-24 and 33, directed to methods of modulating glucose metabolism

Claims 18-24 and 33 are directed to modulating glucose metabolism in an individual. The supporting description in the specification for treating diabetes mellitus applies also to this method. It is respectfully submitted that that no prima facie rejection for lack of enablement has been stated. The Examiner has chosen to lump claims 18-24 and 33 together with claims 1-7, 12 and 17 for the presumed convenience of applying the same rejection to these separate claim

groupings. As applied, the Examiner is rejecting claims 18-24 and 33 on the ground that treatment of diabetes mellitus is not enabled. However, claims 18-24 and 33 are not directed to a method of diabetes mellitus treatment.

Thus, the rejection is clearly deficient on its face, over and above the deficiencies already discussed with respect to claims 1-7, 12 and 17. Furthermore, as no analysis of the Wands factors has been made, Appellant has nothing to rebut. Because the Examiner has failed to meet the burden of challenging enablement of claims 18-24 and 33, Appellant respectfully requests that the rejection be reversed.

The specification provides an enabling disclosure for Claims 25-32, directed to methods of inhibiting the expression of PEPCK

Claims 25-32 are directed to a method for inhibiting expression of phosphoenolpyruvate carboxylkinase (PEPCK) enzyme in an individual. The supporting description in the specification for treating diabetes mellitus applies also to this method. It is respectfully submitted that that no prima facie rejection for enablement has been stated. The Examiner has chosen to lump claims 25-32 together with claims 1-7, 12 and 17 for the presumed convenience of applying the same rejection to these separate claim groupings. As applied, the Examiner is rejecting claims 25-32 on the ground that treatment of diabetes mellitus is not enabled. However, claims 25-32 are not directed to a method of diabetes mellitus treatment.

Thus, the rejection is clearly deficient on its face, over and above the deficiencies already discussed with respect to claims 1-7, 12 and 17. Furthermore, as no analysis of the Wands factors has been made, Appellant has nothing to rebut. Because the Examiner has failed to meet

the burden of challenging enablement of claims 25-32, Appellant respectfully requests that the rejection be reversed.

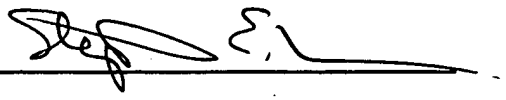
Therefore, because the claimed invention is supported by an enabling disclosure that meets the standard under 35 U.S.C. §112, first paragraph, Appellant respectfully requests that the rejection be withdrawn or reversed.

Conclusion

For the reasons discussed above, the instant claims are in condition for allowance, and Appellant respectfully request that the rejections be withdrawn or reversed.

Respectfully submitted,

Date: April 27, 2004

By 

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Appendix A: Text of the Claims Involved in the Appeal

1. (Previously presented) A method for treating an individual suffering from diabetes mellitus, said method comprising administering an effective amount of a compound which inhibits binding of CREB to CBP.

2 (Original) A method according to claim 1 wherein said treatment of diabetes mellitus ameliorates hyperglycemia.

3. (Original) A method according to claim 2 wherein gluconeogenesis is modulated.

4. (Original) A method according to claim 3 wherein transcription of PEPCK is inhibited.

5. (Previously presented) A method according to claim 2 wherein transcription of the glucagon gene is inhibited.

6. (Previously presented) A method according to claim 1 wherein said individual is a human.

7. (Previously presented) A method according to claim 1 wherein said administering is accomplished by oral, intravenous, subcutaneous, intramuscular or intracutaneous mode of administration.

12. (Previously presented) A method for treating an individual suffering from diabetes mellitus, comprising administering an effective amount of a compound which disrupts complex comprising cyclic AMP response element binding protein (CREB) and CREB binding protein (CBP), said compound identified by a method comprising:

(a) contacting a modified host cell with a test compound, wherein said modified host cell comprises:

a first fusion protein comprising a GAL4 DNA binding domain, operatively

associated with the kinase-inducible domain (KID) of CREB,

a second fusion protein comprising an activation domain, operatively associated with the CREB binding domain (KIX) of CBP, and

a reporter construct comprising a GAL4 response element operatively linked to a reporter gene; and

(b) selecting those test compounds which cause reduced expression of the reporter gene product, wherein said compounds are identified as disrupting complex comprising CREB and CBP.

17. (Previously presented) A method for treating an individual suffering from diabetes mellitus, comprising administering an effective amount of a compound which disrupts complex comprising cyclic AMP response element binding protein (CREB) and CREB binding protein (CBP), said compound identified by a method comprising:

(a) contacting a modified host cell with a test compound, wherein said modified host cell comprises:

a first fusion protein comprising an activation domain, operatively associated with the kinase-inducible domain (KID) of CREB,

a second fusion protein comprising a GAL4 DNA binding domain operatively associated with the CREB binding domain (KIX) of CBP, and

a reporter construct comprising a GAL4 response element operatively linked to a reporter gene; and

(b) selecting those test compounds which cause reduced expression of the reporter gene product, wherein said compounds are identified as disrupting complex comprising CREB and CBP.

18. (Previously presented) A method for modulating glucose metabolism in an individual, said method comprising administering an effective amount of a compound which inhibits binding of CREB to CBP.

19. (Previously presented) A method according to claim 18 wherein said modulating glucose metabolism results in decreased serum glucose.

20. (Previously presented) A method according to claim 18 wherein said modulating glucose metabolism results in decreased gluconeogenesis.

21. (Previously presented) A method according to claim 20 wherein transcription of PEPCK is inhibited.

22. (Previously presented) A method according to claim 20 wherein transcription of the glucagon gene is inhibited.

23. (Previously presented) A method according to claim 18 wherein said individual is a human.

24. (Previously presented) A method according to claim 18 wherein said administering is accomplished by oral, intravenous, subcutaneous, intramuscular or intracutaneous mode of administration.

25. (Previously presented) A method for inhibiting expression of phosphoenolpyruvate carboxykinase (PEPCK) enzyme in an individual, said method comprising administering an effective amount of a compound which inhibits binding of CREB to CBP.

26. (Previously presented) A method according to claim 25 wherein said inhibiting PEPCK enzyme expression results in decreased serum glucose.

27. (Previously presented) A method according to claim 25 wherein said inhibiting PEPCK enzyme expression results in decreased gluconeogenesis.

28. (Previously presented) A method according to claim 27 wherein transcription of

PEPCK is inhibited.

29. (Previously presented) A method according to claim 27 wherein transcription of the glucagon gene is inhibited.

30. (Previously presented) A method according to claim 25 wherein said individual is a human.

31. (Previously presented) A method according to claim 30 wherein said individual is suffering from diabetes mellitus.

32. (Previously presented) A method according to claim 25 wherein said administering is accomplished by oral, intravenous, subcutaneous, intramuscular or intracutaneous mode of administration.

33. (Previously presented) A method according to claim 23 wherein said individual is suffering from diabetes mellitus.